AMENDMENTS

Amendments to the Claims:

Pursuant to 37 C.F.R. 1.121 the following is a complete listing of the claims of the present application and replaces all previous versions.

1.-42. (canceled)

43. (new) A method of inhibiting Flt4 receptor tyrosine kinase (Flt4) function in a mammalian organism with a neoplastic disease, comprising the step of administering to said mammalian organism a composition,

wherein said neoplastic disease is a breast carcinoma characterized by expression of Flt4 in vascular endothelial cells,

wherein said composition comprises an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in blood vascular endothelial cells of said organism, and

wherein said composition is administered in an amount effective to inhibit Flt4-mediated proliferation of said vascular endothelial cells, thereby inhibiting Flt4-mediated proliferation of said vascular endothelial cells.

44. (new) A method according to claim 43 wherein said organism is human.

45. (new) A method according to claim 43 wherein said inhibitor comprises a polypeptide selected from the group consisting of:

(a) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment thereof;

(b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof;

(c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment thereof;

(d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and

(e) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

46. (new) A method according to claim 43, wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

47. (new) A method according to claim 46 wherein said blood vascular endothelial marker antigen is selected from the group consisting of PAL-E, VEGFR-1, and VEGFR-2.

48. (new) A method according to claim 46 wherein said inhibitor further comprises an anti-neoplastic agent conjugated to said bispecific antibody.

49. (new) A method for antagonizing the function of Flt4 receptor tyrosine kinase (Flt4) in an organism, comprising a step of administering to the organism a composition comprising a polypeptide and a pharmaceutically acceptable carrier, wherein the polypeptide is selected from the group consisting of:

(a) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment thereof;

(b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof;

(c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment thereof;

(d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and

(e) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent; and

wherein the organism has a neoplastic disorder characterized by blood vessels comprising endothelial cells that express Flt4.

50. (new) A method for antagonizing the function of Flt4 receptor tyrosine kinase (Flt4) in an organism, comprising a step of administration to the organism a composition comprising a bispecific antibody, or fragment thereof,

wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen; and

wherein said organism has a neoplastic disorder characterized by blood vessels comprising endothelial cells that express Flt4.

51. (new) A method according to claim 49 or 50, wherein the organism is human.

52. (new) A method according to claim 50, wherein said composition further comprises an anti-neoplastic agent conjugated to said antibody or antibody fragment.

53. (new) A method of inhibiting neoplastic cell growth in a mammalian subject, comprising steps of:

(a) screening a mammalian subject to identify a neoplastic disorder characterized by blood vessels that comprise endothelial cells that express Flt4; and

(b) administering a composition to a mammalian subject identified according to step (a) as having a neoplastic disorder characterized by cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, thereby inhibiting Flt4-mediated proliferation of said Flt4-expressing cells, wherein said inhibitor comprises a polypeptide selected from the group consisting of:

(i) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment thereof;

(ii) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof;

(iii) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment thereof; and

(iv) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21);

(v) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

54. (new) A method of inhibiting neoplastic cell growth in a mammalian subject, comprising steps of:

(a) screening a mammalian subject to identify a neoplastic disorder characterized by blood vessels that comprise endothelial cells that express Flt4; and

(b) administering a composition to a mammalian subject identified according to step (a) as having a neoplastic disorder characterized by cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, thereby inhibiting Flt4-mediated proliferation of said Flt4-expressing cells,

wherein said inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

55. (new) A method according to claims 53 or 54, wherein the mammalian subject is human.

56. (new) A method according to claim 54 wherein said blood vascular endothelial marker antigen is selected from the group consisting of PAL-E, VEGFR-1, and VEGFR-2.

57. (new) A method according to claim 54 wherein said inhibitor further comprises an anti-neoplastic agent conjugated to said bispecific antibody.

58. (new) A method according to claims 53 or 54 wherein the screening step comprises:

(a) contacting tissue from the mammalian subject with a composition comprising an antibody or antibody fragment that specifically binds Flt4;

(b) detecting said antibody or antibody fragment bound to cells in said tissue; and

(c) screening for a neoplastic disorder characterized by blod vessels that comprise endothelial cells that express Flt4 from the quantity or distribution of said antibody bound to cells in said tissue.

59. (new) A method according to claim 58 wherein in said screening step, the detection of said antibody or antibody fragment bound to blood vessel endothelial cells is correlated with the presence of a neoplastic disease.

60. (new) The method according to claim 59 wherein said tissue comprises mammary tissue.

61. (new) A method of treating a mammal having breast cancer characterized by blood vessel endothelial cells that express Flt4 tyrosine kinase (Flt4), comprising a step of administering to said mammal a composition, said composition comprising an inhibitor of binding between Flt4 ligand protein and Flt4 expressed in cells of said organism, thereby inhibiting Flt4 function, wherein the inhibitor comprises a member selected from the group consisting of:

(a) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment thereof;

(b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof;

(c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment thereof;

(d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and

(e) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

62. (new) A method of treating a mammal having breast cancer characterized by blood vessel endothelial cells that express Flt4 tyrosine kinase (Flt4), comprising a step of administering to said mammal a composition, said composition comprising an inhibitor of

binding between Flt4 ligand protein and Flt4 expressed in cells of said organism, thereby inhibiting Flt4 function,

wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

63. (new) A method according to claims 61 or 62 wherein said mammal is human.

64. (new) A method according to claim 61 or 62 comprising a screening step preceding the administering step, wherein the screening step comprises screening a human to identify breast cancer characterized by blood vessel endothelial cells expressing Flt4; and

wherein the administering step comprises administering the composition to a human identified by the screening step as having breast cancer characterized by blood vessel endothelial cells expressing Flt4.

65. (new) A method for treating a neoplastic disorder in a mammalian subject, comprising the steps of:

(a) screening a mammalian subject to identify a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4 receptor tyrosine kinase (Flt4); and

(b) administering a composition to a mammalian organism identified according to step (a) as having a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4, to inhibit Flt4 mediated proliferation of said Flt4-expressing cells,

wherein the composition comprises a means for inhibiting Flt4 function in mixture with a pharmaceutically acceptable diluent, adjuvant, or carrier.

66. (new) A method according to claim 65, wherein the mammalian subject is human.

67. (new) A method according to claim 66, wherein the means for inhibiting comprises a member selected from the group consisting of:

(a) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment thereof;

(b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof;

(c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment thereof;

(d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and

(e) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

68. (new) A method according to claim 66, wherein the means for inhibiting comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

69. (new) A method according to claim 68 wherein said blood vascular endothelial marker antigen is selected from the group consisting of PAL-E, VEGFR-1, and VEGFR-2.

70. (new) A method according to claim 68 wherein the means for inhibiting further comprises an anti-neoplastic agent conjugated to said bispecific antibody.

71. (new) A method of inhibiting proliferation of blood vessel endothelial cells in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessel endothelial cells, comprising the step of administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in blood vessel endothelial cells of said organism, thereby inhibiting Flt4-mediated proliferation of the blood vessel endothelial cells, wherein said inhibitor comprises a polypeptide selected from the group consisting of:

(a) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment thereof;

(b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof;

(c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment thereof;

(d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and

(e) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

72. (new) A method of inhibiting proliferation of blood vessel endothelial cells in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessel endothelial cells, comprising the step of administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in blood vessel endothelial cells of said organism, thereby inhibiting Flt4-mediated proliferation of the blood vessel endothelial cells,

wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

73. (new) A method of inhibiting proliferation of endothelial cells in a human organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in endothelial cells, comprising the step of administering to said human organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in endothelial cells of said organism, thereby inhibiting Flt4-mediated proliferation of the cells, wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

74. (new) A method according to claim 72 or 73, wherein said blood vascular endothelial marker antigen is selected from the group consisting of PAL-E, VEGFR-1, and VEGFR-2.

75. (new) A method according to claim 72 or 73, wherein said inhibitor further comprises an anti-neoplastic agent conjugated to said bispecific antibody.

76. (new) A method according to claim 72 or 73, wherein the disease is a tumor characterized by blood vessels with endothelial cells expressing Flt4.

77. (new) A method according to claim 66, wherein the disease is a breast carcinoma characterized by expression of Flt4 in vascular endothelial cells.

78. (new) A method of inhibiting proliferation of endothelial cells in a human organism having a breast carcinoma characterized by expression of Flt4 tyrosine kinase (Flt4) in vascular endothelial cells, comprising the step of administering to said human organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in endothelial cells of said organism, thereby inhibiting Flt4-mediated proliferation of the cells, wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

79. (new) A method according to claim 78 wherein said blood vascular endothelial marker antigen is selected from the group consisting of PAL-E, VEGFR-1, and VEGFR-2.

80. (new) A method according to claim 78 wherein said inhibitor further comprises an anti-neoplastic agent conjugated to said bispecific antibody.

81. (new) A method of inhibiting genesis of blood vessels in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessels, comprising the step of administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4-mediated proliferation of the cells, wherein said inhibitor comprises a member selected from the group consisting of:

(a) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment thereof;

(b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof;

(c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment thereof;

(d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and

(e) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

82. (new) A method of inhibiting genesis of blood vessels in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessels, comprising the step of administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4-mediated proliferation of the cells,

wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

83. (new) A method according to claim 81 or 82 wherein said organism is human.

84. (new) A method according to claim 83, wherein the human has a tumor characterized by blood vessels that express Flt4.

85. (new) A method of inhibiting the growth or the metastatic spread of a tumor in a mammalian organism, comprising steps of administering to a mammalian organism a composition that comprises an inhibitor of the binding of an Flt4 ligand protein to Flt4 receptor tyrosine kinase (Flt4) expressed in cells of said organism, wherein the mammalian organism has a tumor characterized by blood and lymphatic vessels that express Flt4, and wherein the composition inhibits proliferation of the blood and lymphatic vessels, thereby inhibiting growth or metastatic spread of the tumor, wherein the inhibitor comprises a member selected from the group consisting of:

(a) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment thereof;

(b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof;

(c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment thereof;

(d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and

(e) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

86. (new) A method of inhibiting the growth or the metastatic spread of a tumor in a mammalian organism, comprising steps of administering to a mammalian organism a composition that comprises an inhibitor of the binding of an Flt4 ligand protein to Flt4 receptor tyrosine kinase (Flt4) expressed in cells of said organism, wherein the mammalian organism has a tumor characterized by blood and lymphatic vessels that express Flt4, and wherein the composition inhibits proliferation of the blood and lymphatic vessels, thereby inhibiting growth or metastatic spread of the tumor,

wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

87. (new) A method according to claim 85 or 86, comprising a diagnosing step prior to the administering step, said diagnosing step comprising identifying a patient having a tumor characterized by blood vessels that express Flt4.

88. (new) A method according to claim 85 or 86, comprising a diagnosing step prior to the administering step, said diagnosing step comprising identifying a patient having lymph node metastasis of a tumor, wherein the lymph node comprises cells expressing Flt4.

89. (new) A method of inhibiting neoplastic cell growth in a human subject, comprising steps of:

(a) screening a human subject to identify a neoplastic disorder characterized by blood vessels that comprise endothelial cells expressing Flt4 receptor tyrosine kinase (Flt4); and

(b) administering a composition to a human subject identified according to step (a) as having a neoplastic disorder characterized by blood vessels that comprise endothelial cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, thereby inhibiting Flt4-mediated proliferation of said Flt4-expressing cells, wherein the inhibitor comprises a member selected from the group consisting of:

(i) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment thereof;

(ii) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof;

(iii) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment thereof;

(iv) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and

(v) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

90. (new) A method of inhibiting neoplastic cell growth in a human subject, comprising steps of:

(a) screening a human subject to identify a neoplastic disorder characterized by blood vessels that comprise endothelial cells expressing Flt4 receptor tyrosine kinase (Flt4); and

(b) administering a composition to a human subject identified according to step (a) as having a neoplastic disorder characterized by blood vessels that comprise endothelial cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, thereby inhibiting Flt4-mediated proliferation of said Flt4-expressing cells,

wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

91. (new) A method of inhibiting neoplastic cell growth in a mammalian subject, comprising steps of:

(a) screening a mammalian subject to identify a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4 receptor tyrosine kinase (Flt4), wherein the screening comprises

(i) contacting tissue from the mammalian subject with a composition comprising an antibody or antibody fragment that specifically binds Flt4;

(ii) detecting said antibody or antibody fragment bound to cells in said tissue; and

(iii) screening for a neoplastic disorder from the quantity or distribution of said antibody or antibody fragment bound to cells in said tissue, wherein the detection of said antibody or antibody fragment bound to blood vessel endothelial cells is correlated with the presence of a neoplastic disease; and

(b) administering a composition to a mammalian subject identified according to step (a) as having a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, thereby inhibiting Flt4-mediated proliferation of said Flt4-expressing cells, wherein the inhibitor comprises a member selected from the group consisting of:

(i) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment thereof;

(ii) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof;

(iii) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment thereof;

(iv) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and

(v) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

92. (new) A method of inhibiting neoplastic cell growth in a mammalian subject, comprising steps of:

(a) screening a mammalian subject to identify a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4 receptor tyrosine kinase (Flt4), wherein the screening comprises

(i) contacting tissue from the mammalian subject with a composition comprising an antibody or antibody fragment that specifically binds Flt4;

(ii) detecting said antibody or antibody fragment bound to cells in said tissue; and

(iii) screening for a neoplastic disorder from the quantity or distribution of said antibody or antibody fragment bound to cells in said tissue, wherein the detection of said antibody or antibody fragment bound to blood vessel endothelial cells is correlated with the presence of a neoplastic disease; and

(b) administering a composition to a mammalian subject identified according to step (a) as having a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, thereby inhibiting Flt4-mediated proliferation of said Flt4-expressing cells,

wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

93. (new) A method according to claim 91 or 92, wherein said tissue comprises mammary tissue.